MEGDEL Syndrome: Expanding the Phenotype and New Mutations

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Abstract

3-MEthylGlutaconic aciduria, Deafness, Encephalopathy, neuroradiological evidence of Leigh-like disease (MEGDEL syndrome) was initially described in four children with additional features of defective oxidative phosphorylation. Loss of functional variants in the *SERAC1* gene was later reported in relation with this disorder of phospholipid remodeling. We describe a girl born after a pregnancy complicated by intrauterine growth retardation. In the neonatal period, she presented hypotonia, lethargy, weak reflexes, transient hypoglycemia, and elevated transaminases. Magnetic resonance imaging (MRI) performed at 12 days of life showed bilateral basal ganglia alterations suggestive of Leigh syndrome. She progressed with failure to thrive, severe delay of developmental milestones, axial hypotonia, spastic tetraparesis and dystonic movements. Investigations disclosed hyperlactacidemia, and the urinary organic acids revealed high levels mainly of 3-methylglutaconic acid. Muscle biopsy showed decreased activity of several complexes of the respiratory chain. Compound heterozygosity for two previously unreported variants in *SERAC1* leads to the diagnosis of MEGDEL syndrome. Unlike other patients, this child presents very early MRI alterations and manifests no deafness.

Keywords
- MEGDEL syndrome
- SERAC1 gene
- 3-methylglutaconic aciduria
- mitochondrial disorder
- Leigh syndrome

Introduction

3-MEthylGlutaconic aciduria, Deafness, Encephalopathy, Leigh-like (MEGDEL) syndrome (MIM #614739) or SERAC1 defect is one of the several inborn errors of metabolism with 3-methylglutaconic aciduria (3-MGA-uria) as a discriminative feature, a heterogeneous group of disorders.[1–5] Here, we expand the clinical and genetic spectrum by describing one individual early magnetic resonance imaging (MRI) Leigh syndrome and without hearing loss harboring previously unreported variants in *SERAC1* gene.[3,6–8]

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Case Report

This girl was born by cesarean delivery at 39 weeks of unrelated parents of European ancestry. No relevant familial clinical history was reported. Despite intrauterine growth retardation, the pregnancy was uneventful. Her birth weight was 2,240 g, height 44.5 cm, and head circumference 31.5 cm (all below p3). Apgar score was 9 and 10 at 1 and 5 minutes, respectively. After 30 minutes of birth, she started grunting, showing irritability, decreased reflexes, and drowsiness. She needed parenteral nutrition due to progressive feeding difficulties and progressed to hypotonia and lethargy.

Transient hypoglycemia (1.4 mmol/L; reference values [RV]: 3.5–5.6) and mildly elevated transaminases were detected. Blood gas analysis at 48 hours of life revealed metabolic acidosis (pH 7.15, bicarbonate 10.3 mmol/L) and increased lactate (6.5 mmol/L; RV: 0.9–2.3). There was no evidence of infection. She was treated with bicarbonate, antibiotics, and artificial ventilation on day 3 of life. Due to worsening of symptoms on day 4 of life, with constant groaning, breathing difficulty, abdominal distension, food refusal, abundant brownish secretions in the gastric aspirate, and worsening of consciousness level to coma, she was transferred to the neonatal intensive care unit of a specialized metabolic center.

She was pale, not well perfused, mildly jaundiced, presenting groaning, few active movements, slow reactions to stimuli, decreased neurological reflexes, and no peripheral hypotonia or clonus and rapidly progressed to coma. She did not present dysmorphisms or hepatomegaly. The electroencephalogram revealed depressed, irregular, and moderately reactive features, abundant multifocal paroxysmal activity and several electrographic seizures. The computed tomography scan suggested diffuse cerebral edema.

From day 7 of life onwards, she presented progressive improvement of her neurological status with an increase in consciousness and reflexes despite persistent lactic acidemia (3.1 mmol/L) and hyperammonemia (182.8 µmol/L; RV: < 50), without hypoglycemia. Urinary organic acids showed 3-MGA-uria (107 µmol/mmolCr; RV: 0–9, ►**Table 1**).

MRI of the brain was performed on day 12 of life (►**Fig. 1**) and revealed symmetric bilateral lesions involving the caudate nucleus, the pallidum, and the interior part of the putamen, white matter hyperintensities on T2 and hypointense on T1, with pallidal lesions with restricted diffusion. A high lactate peak at the basal ganglia, pulvinar thalamus, and white matter was also observed.

Follow-up of the child showed marked failure to thrive, severe delay of developmental milestones, microcephaly, spastic tetraparesis, and dystonia. Later sleeping disturbances were frequently reported, and at the age of 6 years, the first seizure suggested myoclonic epilepsy, which was successfully treated with levetiracetam.

Ophthalmological observation and hearing screening were unremarkable. No follow-up MRI is available.

A muscle biopsy performed at the age of 1 year showed: fiber size variability, overload of periodic acid-Schiff-positive material in some fibers; cytochrome oxidase/succinic dehydrogenase (COX/SDH) staining hyperchromatic aggregates to the periphery and the absence of COX-negative fibers. The activity of the respiratory chain showed decreased activity of several complexes: II (37.9%), IV (34.0%), V (20.1%), and segment II + III (23.2%).

A leucine-loading test was performed as described by Wortmann et al.[9] No significant increase in 3-MGA-uria was seen after leucine loading, virtually excluding 3-methylglutaconyl-CoA hydratase deficiency (AUH) defect (►**Table 1**).

Sanger Sequencing of *SERAC1* gene revealed two previously unreported variants c.310A > T (p.Lys104*) and c.609 + 5_609 + 8del suggesting the diagnosis of MEGDEL syndrome.

Presently, at the age of 8 years, the patient can fixate and follow, is interested in her surroundings, smiles, reacts to her name or other sounds, babbles, looks for hidden objects, shows difficulties in manipulation, but throws toys to the floor. Although head control is still unstable, she can roll but not sit unaided. She has sleeping problems such as difficulty to fall asleep and frequent awakening during the night. Eye movements are normal, but she also presents myoclonic epilepsy, frequent dystonic movements of limbs and head and marked spastic tetraparesis.

Discussion

Since MEGDEL syndrome was first described,[2] more than 25 cases have been reported. These patients share a strikingly homogenous clinical phenotype, with signs and symptoms beginning during their newborn period or infancy.[3,6–8,10,11] These include elevated urinary 3-MGA, deafness, neuroradiological evidence of Leigh-like disease,[12] neonatal hypoglycemia, bilateral optic nerve atrophy, microcephaly, myoclonic epilepsy, dystonia, and disturbed oxidative phosphorylation. In addition, transient hepatic involvement has

Table 1 Biochemical analysis of urinary organic acids during neonatal period and leucine loading test

	Reference value µmol/mmolCr	6 d of life	Leucine loading test		
			Basal	After 1 h	After 24 h
3-hydroxyisovaleric acid	0–18	66	33	86	130
3-methylglutaric acid	0–0.1	15	28	24	33
3-methylglutaconic acid	0–9	107	187	179	234
3-hydroxy-3-methylglutaric acid	15–43	98	35	39	26

Abbreviation: Cr, creatinine.
Note: Loading test with 100 mg/kg of leucine orally reveals only a 1.25 increase of 3-MGA excluding an AUH defect.

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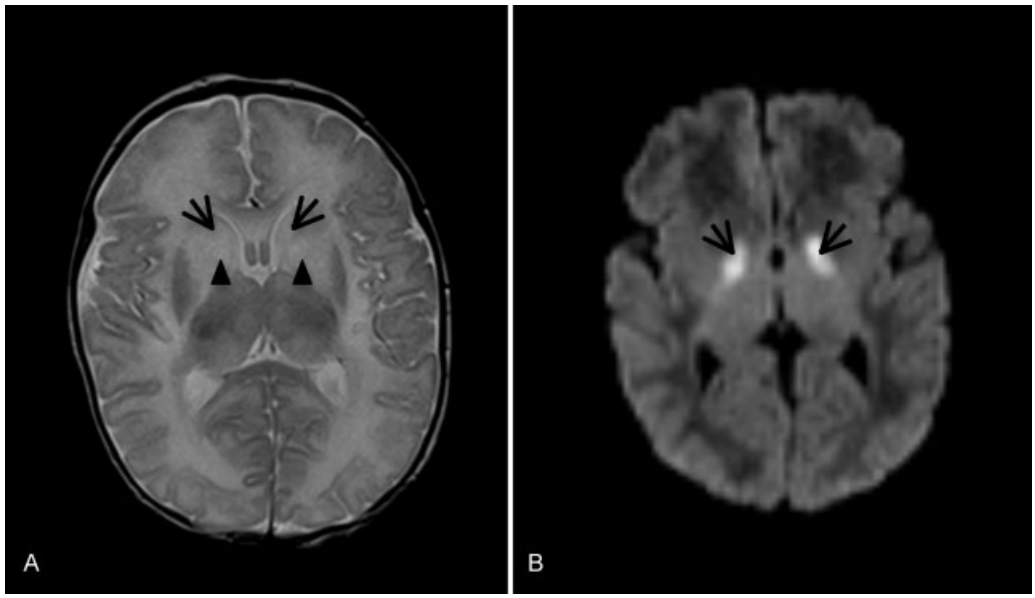

Fig. 1 Axial T2-weighted and diffusion MRI images of the brain performed 12 days after birth depicting Leigh-like changes, with (**A**) bilateral increased signal change in the caudate nucleus (black arrow), globus pallidus, and medial putamen (arrowhead) and with (**B**) pallidal lesions with restricted diffusion (arrows). MRI, magnetic resonance imaging.

been described leading to a possible designation of MEGDEL syndrome.[11]

Here, we report a case of MEGDEL syndrome, with very early MRI alterations, already detected 12 days after birth. This is much earlier than what has been reported for MRI alterations in MEGDEL syndrome.[11]

Another important finding is that this patient displays no deafness at the age of 8 years. This has only been reported once in this disorder and we cannot exclude that this will develop later in life.[7]

Both variants in SERAC1 detected in this affected individual have not been described previously, but prediction models (Alamut Visual software v.2.7.1) support their pathogenicity. The nonsense variant c.310A > T (p.Lys104*) is predicted to interrupt the reading frame by a premature stop codon, which may lead to an impairment in the targeting of the produced mRNA for nonsense-mediated decay. The intronic c.609 + 5_609 + 8del variant, also classified as a variant of unknown pathogenicity, is close to the donor splice site of exon 7 and therefore a skip of exon 7 is predicted.

In conclusion, the individual presented here expands the clinical spectrum with early detectable basal ganglia lesions and absence of deafness and extends the genetic spectrum.

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